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Penicillin concentrations in cerebrospinal fluid after different treatment regimens for syphilis

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SUMMARY The concentrations of penicillin in the cerebrospinal fluid (CSF) were compared simultaneously with those in the serum in 17 patients with syphilis. The antibiotic concentrations were measured by the agar well diffusion method. There were no detectable concentrations of penicillin in the CSF after administration of benzathine penicillin 2·4 megaunits, benzathine penicillin 7·2 megaunits, procaine penicillin in aluminium monostearate (PAM) 12 megaunits, or aqueous procaine penicillin G 2·4 megaunits. Only after high doses of aqueous penicillin G 24 megaunits daily or aqueous penicillin G 2 megaunits daily together with oral probenecid 2 g daily was penicillin detectable in the CSF. The concentrations after the latter regimen were the highest and much higher than the minimum inhibitory concentration for *Treponema pallidum*.

Introduction

Even though penicillin is the drug of choice in the treatment of syphilis,[1] the results in the late stages, especially in neurosyphilis, are still not perfect.[2 3] Viable treponemes have been detected after treatment with the recommended dosage of penicillin.[4-7]

Mohr *et al*[8] reported that 12 of their 13 patients who received benzathine penicillin G intramuscularly (im) for the treatment of neurosyphilis had no detectable penicillin in the cerebrospinal fluid (CSF) and suggested that the drug might have to be given intravenously (iv) to produce an effective concentration in the CSF. Yoder[9] reported that in one patient treated with procaine penicillin G 600 000 IU by daily intramuscular injection the drug concentration in the CSF after five days was less than 0·017 IU/ml. The minimum fully treponemicidal concentration of penicillin recommended by the World Health Organisation is 0·03 IU (0·018 μg) per ml.[10] For effective treatment of neurosyphilis it seems logical that this concentration should be achieved in the CSF. Boger *et al*[11] found that by giving penicillin intramuscularly together with oral carinamide, which inhibits renal tubular excretion of penicillin, the concentrations in the CSF of patients with neurosyphilis were higher than when penicillin was given alone.

The purpose of this study was to measure the penicillin concentrations in the CSF of patients with syphilis after different recommended dosages of penicillin and to compare them with those after a new regimen using parenteral penicillin together with oral probenecid.

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Patients and methods

From January 1978 all patients who were diagnosed as having secondary, latent, and late syphilis and neurosyphilis at Ramathibodi Hospital were studied. The diagnosis was based on history and clinical examination together with serological and CSF findings. All patients were informed of the study and the necessity for repeated lumbar punctures. Signed consent was obtained.

SEROLOGICAL TESTS

The Venereal Disease Research Laboratory (VDRL) test was performed by the standard method,[12] the fluorescent treponemal antibody absorption (FTA-ABS) test by the method of Hunter *et al*,[13] and the *Treponema pallidum* haemagglutination assay (TPHA) by the method of Rathlev.[14] The CSF-FTA, CSF-FTA-ABS, and CSF-FTA-IgM tests were performed on undiluted specimens.

TABLE I *Penicillin concentrations in serum and CSF of 17 patients with syphilis*

	Treatment regimen		*Penicillin concentration*		
Case No	*Drug*	*Dose*	*Time measured (days after last dose)*	*Serum (IU/ml)*	*CSF (IU/ml)*
1	Benzathine penicillin	2·4 mu (im)	3rd	0·043	0
2	Benzathine penicillin	2·4 mu (im)	3rd	0·007	0
3	Benzathine penicillin	7·2 mu (im) (2·4 mu × 3 doses)	3rd	0·016	0
4	Benzathine penicillin	7·2 mu (im) (2·4 mu × 3 doses)	3rd	0·45	0
5	Benzathine penicillin	7·2 mu (im) (2·4 mu × 3 doses)	3rd	0·45	0
6	Benzathine penicillin	7·2 mu (im) (2·4 mu × 3 doses)	3rd	0·255	0
7	PAM and Benzathine penicillin	4·8 mu (im) 4·8 mu (im)	3rd	0·023	0
8	PAM	12 mu (im) (1·2 mu × 10 doses)	30 min	0·991	0
9	Aqueous penicillin G	400 000 IU (iv) (4 hrly × 10 days)	30 min (after 1st dose) 15 min (before last dose)	1·015 0·962	0 0
10	Aqueous penicillin G	400 000 IU (iv) (4 hrly × 7 days)	30 min (after last dose) 15 min (before last dose)	2·979 0·160	0 0
11	Aqueous penicillin G	4 mu (iv) (4 hrly × 10 days)	30 min (after 1st dose) 15 min (before next dose) 15 min (before last dose)	56·05 128·25 3·453	0·044 0·355 0·579
12	Aqueous penicillin G + Probenecid	500 000 IU (iv) 500 mg (orally) (6 hrly × 20 days)	5th (of treatment)* 10th (of treatment)* 20th (of treatment)*	6·05 6·08 8·238	2·838 1·611 1·84
13	Aqueous penicillin G + Probenecid	500 000 IU (iv) 500 mg (orally) (6 hrly × 20 days)	5th (of treatment)* 10th (of treatment)* 20th (of treatment)*	3·565 4·835 5·787	0·414 0·191 0·231
14	Aqueous penicillin G + Probenecid	500 000 IU (iv) 500 mg (orally) (6 hrly × 20 days)	5th (of treatment)* 10th (of treatment)*	3·7 4·0	0·45 0·5
15	Aqueous penicillin G + Probenecid	500 000 IU (iv) 500 mg (orally) (6 hrly × 20 days)	5th (of treatment)* 10th (of treatment)* 20th (of treatment)*	4·35 4·9 1·54	0·447 0·3 0·12
16	Aqueous penicillin G + Probenecid	500 000 IU (iv) 500 mg (orally) (6 hrly × 20 days)	5th (of treatment)* 10th (of treatment)* 20th (of treatment)*	3·48 4·8 2·1	0·35 0 0
17	Aqueous penicillin G + Probenecid	500 000 IU (iv) 500 mg (orally) (6 hrly × 20 days)	5th (of treatment)* 20th (of treatment)*	1·85 2·5	0 0·85

*Three hours after first dose
mu = megaunits
PAM = procaine penicillin in aluminium monostearate

SAMPLE COLLECTION

Serum and CSF samples were collected simultaneously before, during, and after treatment according to the regimen shown in table I. In patients who received benzathine penicillin G the samples were collected on the third day after injection whereas in those who received high-dose aqueous penicillin G they were collected 30 minutes after the first dose and 15 minutes before the last dose. In patients treated with aqueous penicillin G and oral probenecid the specimens were collected on the fifth, tenth, and twentieth days of treatment three hours after the first dose of that day.

PENICILLIN CONCENTRATIONS

The penicillin concentrations in the serum and CSF were measured by microbiological assay using an agar well diffusion method with *Bacillus subtilis* ATCC 6633 as the test organism.[15] The accuracy of this method is more than 95% confidence limit. The minimum concentration of penicillin that can be detected by this method is 0·006 IU/ml. The serum and CSF specimens were stored at −20°C if the assay could not be carried out immediately.

CLINICAL PRESENTATION

The clinical presentation of the 17 patients studied is summarised in table II. Seven patients had early syphilis (cases 1, 3, 5, 6, 7, 13, and 17), three occlusive vascular diseases (cases 2, 11, and 12), one epilepsy (case 16), one general paralysis of the insane (case 15), and one tabes dorsalis (case 10), while three were asymptomatic (cases 4, 9, and 14) and one had congenital syphilis with chronic urticaria (case 8).

TREATMENT

The treatment schedules are given in table I. Case 7 was given a combination of procaine penicillin and aluminium monostearate (PAM) and benzathine penicillin G (total 9·6 megaunits im) because of panniculitis after the second dose of PAM. The combination of aqueous penicillin G 500 000 IU iv together with probenecid 500 mg orally given 30 minutes before injection every six hours for 20 days was studied in cases 12-17.

Results

The penicillin concentrations in serum and CSF of the 17 patients studied are shown in table I. None had detectable penicillin concentrations in the control specimens. In those patients who received benzathine penicillin G the serum concentrations on the third day after the last dose ranged from 0·0067 to 0·45 IU/ml whereas there were no detectable concentrations in the CSF. With PAM the serum concentration after 12 megaunits was higher (0·9912 IU/ml) but still no penicillin was detected in the CSF. Even with aqueous penicillin G 400 000 IU iv, which gave sufficiently high serum concentrations

TABLE II *Clinical presentation, serological test results, and CSF findings in 17 patients with syphilis*

				Serum			*CSF*				
Case No	*Sex*	*Age (years)*	*Clinical presentation*	*VDRL test (titre)*	*TPHA test*	*FTA-ABS test*	*WC* (/mm³)*	*Protein (g/l)*	*FTA test*	*FTA-ABS test*	*FTA-IgM test*
1	M	25	Skin rash	1/32	R	R	1	0·68	R	NR	NR
2	F	47	Cranial nerve III palsies	1/1	R	ND	0	0·25	NR	NR	NR
3	M	22	Skin rash	1/16	ND	R	0	0·48	R	NR	NR
4	M	22	Asymptomatic	1/2	R	R	1	0·38	R	NR	NR
5	M	25	Alopecia	1/16	R	R	1	0·54	R	NR	NR
6	M	25	Skin rash	1/64	ND	R	0	0·45	NR	NR	NR
7	F	25	Alopecia	1/64	R	R	1	0·52	R	NR	NR
8	F	29	Chronic urticaria	1/2	ND	R	5	0·56	NR	NR	NR
9	M	28	Asymptomatic	1/4	R	R	5	0·52	R	NR	NR
10	M	48	Tabes dorsalis	1/4	ND	ND	46	0·40	R	R	NR
11	F	68	Cranial nerves III and IV palsies	1/8	R	R	12	0·22	R	NR	NR
12	F	70	Brain stem vascular disease	1/16	R	R	2	0·49	NR	NR	NR
13	M	24	Alopecia, absent deep tendon reflexes	1/64	R	R	0	0·36	R	R	NR
14	M	50	Asymptomatic	1/32	R	R	0	0·54	R	R	R
15	M	54	General paralysis of the insane	1/2	R	R	4	0·58	R	R	NR
16	M	46	Epilepsy	1/1	R	R	†	†	R	NR	NR
17	F	38	Skin rash	1/128	R	R	0	0·52	R	R	R

*WC = White cells (lymphocytes)
† Data not recorded
R = reactive, NR = non-reactive, ND = not done

(1·015-2·979 IU/ml at 30 minutes after the first dose), no penicillin was detectable in the CSF.

Only with a high dose of aqueous penicillin—that is, 4 megaunits iv every four hours, giving a serum concentration of 56·05 IU/ml at 30 minutes after the first dose—was the drug detected in the CSF (0·044 IU/ml). With this regimen—even at 15 minutes before the last dose, which theoretically was the time of low serum concentration (3·453 IU/ml)—a high penicillin concentration could still be detected in the CSF (0·579 IU/ml).

Interestingly, patients receiving aqueous penicillin G 500 000 IU iv with oral probenecid 500 mg 30 minutes before injection every six hours showed high serum concentrations ranging from 1·85 to 6·05 IU/ml (mean 3·833 IU/ml) with simultaneous CSF concentrations ranging from 0 to 2·838 IU/ml (mean 0·75 IU/ml) at three hours after the first dose of penicillin on the fifth day of treatment. The mean CSF concentrations of penicillin at three hours after the first dose on the tenth and twentieth days were 0·521 and 0·608 IU/ml respectively whereas the simultaneous serum concentrations were 4·923 and 4·033 IU/ml respectively.

The CSF concentrations as the mean percentage of the serum concentrations were 19·57% on the fifth day, 10·58% on the tenth day, and 15·08% on the twentieth day.

Discussion

Although penicillin is still the drug of choice for the treatment of all stages of syphilis, many reports[16-20] of failure to eradicate the organism or to halt the progression of the disease in later stages—in particular, neurosyphilis—have been of recent interest. In some reports methodological difficulties raised uncertainties,[21] but there were at least six which documented success in producing darkfield-positive lesions containing typical treponemes in animals after the inoculation of materials from penicillin-treated patients with syphilis.[4 6 7 22-24]

Our findings confirm those of Boger *et al*,[11] who found that with aqueous penicillin G 100 000 IU im three-hourly low concentrations of penicillin (ranging from 0·019 to 0·052 IU/ml) could be detected in the CSF by the Rammelkamp serial dilution method, but after the addition of oral carinamide 3 g three-hourly the detectable concentrations of penicillin increased to between 0·026 and 2·5 IU/ml. Carinamide, like probenecid, delays the excretion of penicillin by inhibiting renal tubular function.

In our patients there was no detectable penicillin in the CSF after recommended doses of benzathine penicillin G and PAM or even after aqueous penicillin G 2·4 megaunits iv daily. After high doses of aqueous penicillin G (24 megaunits iv daily) sufficient penicillin could be detected in the CSF but the concentrations were lower than those obtained after aqueous penicillin G (2 megaunits iv daily) together with oral probenecid (2 g daily).

Apart from the benefit of lower doses of penicillin in the new regimen it seems likely that probenecid may have a direct effect on the blood-brain barrier, thus enhancing penetration of penicillin into the central nervous system. This however needs further evaluation.

Recently, Dunlop *et al*,[25] studying 31 patients and using single lumbar punctures to determine the concentration of penicillin in the CSF on different days after treatment but with no control specimens for the penicillin concentration, obtained similar results to ours. Only after aqueous penicillin G 500 000 IU im six hourly together with probenecid 500 mg six hourly by mouth in six of eight patients were treponemicidal concentrations of penicillin in the CSF achieved.

It is logical that treponemicidal concentrations of penicillin in the CSF should be obtained in the treatment of neurosyphilis. However the outcome of treatment with this new regimen compared with those previously used needs a larger number of patients to be studied and a longer period of follow-up before definite benefits can be established.

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